Shaw, D. 2019. The consent form in the Chinese CRISPR study: In search of ethical editing. *Journal of Bioethical Inquiry* 17(1).

Supplementary Material

Appendix 4 Ethics Application

Medical Ethics Approval Application Form

HarMoniCare Shenzhen Women's and Children's Hospital

<table>
<tr><td>Project</td><td colspan="3">CCR5 Gene editing</td><td colspan="2">Duration</td><td colspan="2">March 2017 – March 2019</td></tr>
<tr><td>Classification</td><td colspan="7">Advanced technology / New Project
Class II or III medical technology
Research (√)
Reproductive Medicine
Organ transplantation
Others</td></tr>
<tr><td colspan="8">Applicant Information</td></tr>
<tr><td>Name</td><td>HE JIANKUI</td><td>Sex</td><td>Male</td><td>Education</td><td>Ph.D</td><td>Tel</td><td>18688955436</td></tr>
<tr><td>Research Directions</td><td colspan="7">Genomics</td></tr>
<tr><td>Application Description</td><td colspan="7">CCR5 is the gene which encodes a protein located on the surface of T cell wihch functions as a chemokine receptor for the immune system and plays a role in the binding of T cells to specific tissues and target organs. It regulates the migration, proliferation and immunity of T cells and monocytes or macrophages, and is mainly expressed on the membrane of resting silent T lymphocytes, monocytes, immature dendritic cells and so on. Results of population surveys and clinical studies indicate that individuals with CCR5 32bp-deletions have normal immune and inflammatory responses and are significantly resistant to multiple viral infections; therefore, gene editing on CCR5 may be effective in blocking cholera, smallpox or HIV infection.

Recently Chinese scientists made use of CRISPR-Cas9 to destroy hepatitis B virus. Gene therapy brings hope to rare but deliberating diseases. In February 2017, the US National Academy of Science, Engineering and Medicine released a statement that experimental study on the gene editing of embryos as therapeutics for the treatment of serious diseases is ethically acceptable. This brings hope to the treatment of many serious genetic diseases.

In this study, we plan to use the CRISPR-Cas9 to edit the embryo. Oocytes and sperms were collected from volunteers with HIV infection. CRISPR-Cas9 protein and gRNA are injected into fertilized eggs, and we can select the individual embryos with CCR5 gene edited by preimplantation genetic diagnosis, the edited embryos are transferred to women and pregnancy will follow. The baby born can gain the capability of resistance to HIV infection, smallpox, and cholera.

In early experiments, we have set strict quality control standards for gene editing</td></tr>
</table>

	to fully assess the feasibility of CCR5 editing in embryo from a safety perspective. First of all, the cell lines and animal models (mice, monkeys) were used to conduct rigorous experimental studies on the effects of CCR5 gene editing. In particular, we chose monkeys, the species that is close to humans, as model animals for embryo editing by CRISPR-Cas9 method and assessed for the health status, physiology and neurobehavioral impact of the genetic editing. This design allows the identification of any related diseases due to gene editing. At the same time, we will isolate the embryonic stem cells post gene editing to detect for any abnormality of the proliferation and differentiation. Secondly, a variety of approaches are used to reduce off-target events and mosaic issues. For example, the high-fidelity CAS9 protein and the best sgRNA targeting CCR5 gene was used in combination with whole-genome amplification and genome-wide sequencing to detect off-target events and mosaicity. At the same time, we developed bioinformatics approaches to perform accurate assessment of the potential off-target harm. Finally, the multi-generational effects of gene editing are examined in animal models to explore the health status of the genetically-modified descendants Based on the above described research and experimental results, we designed this study aiming to perform in vitro fertilization using assisted reproductive technology, with the CCR5 gene being edited using CRISPR-Cas9 technology. The edited embryos are compared with the normal fertilized eggs to check for any difference in morphology. At the same time, the single-cell transcriptomics method will be used to compare the differences in transcriptome development between genetically modified embryos and normal embryos. Using PGS / PGD technology, we will perform rigorous genetic diagnosis and screening of the embryos before implantation by single cell whole genome sequencing to confirm that the editing is successful without off-targets and mosaic issues through thorough evaluation. We then choose the best embryo for implantation. During pregnancy, extensive physical examination is conducted and whole genome sequencing to be applied on the early- and mid-term amniotic fluid to make sure that the fetus is normal, until eventually a healthy baby will be born with CCR5 edited. Through this study, we expect to establish a solid technique standard for therapy by gene editing and bring gene editing related therapy to a new level. Ultimately, our research will stand out in the increasingly competitive international application of gene editing technology. This is going to be a great science and medicine achievement ever since the IVF technology which was awarded the Nobel Prize in 2010, and will also bring hope to numerous genetic disease patients.

Approval results	This study complies with the ethic regulations. We Agree to allow the conduct of the study. Signature by all Committee Members with the seal of the Chairman on 7th March 2017